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(54) Title: NOVEL VINYL CARBOXYLIC ACID DERIVATIVES AND THEIR USE AS ANTIDIABETICS ETC.

(57) Abstract: Novel compounds of the general formula (I), the use of these compounds as pharmaceutical compositions, pharmaceutical compositions comprising the compounds and methods of treatment employing these compounds and compositions. The present compounds may be useful in the treatment and/or prevention of conditions mediated by Peroxisome Proliferator-Activated Receptors (PPAR), in particular the PPAR δ subtype.

NOVEL VINYL CARBOXYLIC ACID DERIVATIVES AND THEIR USE AS ANTIDIABETICS ETC

FIELD OF THE INVENTION

The present invention relates to novel vinyl carboxylic acid derivatives, to the use of these compounds as pharmaceutical compositions, to pharmaceutical compositions comprising the compounds and to a method of treatment employing these compounds and compositions. More specifically, the compounds of the invention can be utilised in the treatment and/or prevention of conditions mediated by the Peroxisome Proliferator-Activated Receptors (PPAR), in particular the PPAR δ subtype.

BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potentially lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose

metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid β -oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

PPAR δ activation was initially reported not to be involved in modulation of glucose or triglyceride levels. (Berger et al., *J. Biol. Chem.*, 1999, Vol 274, pp. 6718-6725). Later it has been shown that PPAR δ activation leads to increased levels of HDL cholesterol in db/db mice (Leibowitz et al. FEBS letters 2000, 473, 333-336). Further, a PPAR δ agonist when dosed to insulin-resistant middle-aged obese rhesus monkeys caused a dramatic dose-dependent rise in serum HDL cholesterol while lowering the levels of small dense LDL, fasting triglycerides and fasting insulin (Oliver et al. PNAS 2001, 98, 5306-5311). The same paper also showed that PPAR δ activation increased the reverse cholesterol transporter ATP-binding cassette A1 and induced apolipoprotein A1-specific cholesterol efflux. Taken together these observations suggest that PPAR δ activation is useful in the treatment and

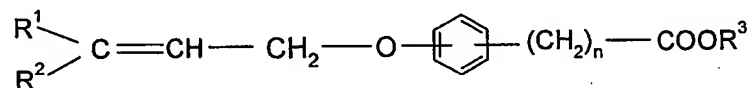
prevention of cardiovascular diseases and conditions including atherosclerosis, hypertriglyceridemia, and mixed dyslipidaemia (PCT publication WO 01/00603 (Chao et al.).

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications
 5 nos. W091/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313, WO 99/16758 and WO 01/00603).

Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of
 10 Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

This indicate that research for compounds displaying various degree of PPAR α , PPAR γ and PPAR δ activation should lead to the discovery of efficacious triglyceride and/or
 15 cholesterol and/or glucose lowering drugs that have great potential in the treatment of diseases such as type 2 diabetes, dyslipidemia, syndrome X (including the metabolic syndrome, i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity), cardiovascular diseases (including atherosclerosis) and hypercholesteremia.

In EP 98 690 the following vinyl carboxylic acid derivatives has been described as
 20 thromboxane A2 synthetase inhibitors:



wherein R¹ is pyridyl, R² is phenyl, thienyl, furyl, naphtyl, benzothienyl or pyridyl, and R³ is hydrogen or lower alkyl.

In WO 00/64888 diaryl acid derivatives and their pharmaceutical compositions are
 25 described as PPAR receptor ligands.

DEFINITIONS

In the structural formulas given herein and throughout the present specification the following terms have the indicated meaning:

The term "C₁₋₈-alkyl" as used herein, alone or in combination, represent a linear or
 30 branched, saturated hydrocarbon chain having the indicated number of carbon atoms. Examples of such groups include, but are not limited to methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C₃₋₆-cycloalkyl" as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the indicated number of carbon atoms. Examples of such groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

5 The term "C₂₋₆-alkenyl" as used herein, represent an olefinically unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl and the like.

10 The term "C₂₋₆-alkynyl" as used herein, represent an unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 1-pentynyl, 2-pentynyl and the like.

15 The term "C₄₋₆-alkenynyl" as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-ynyl, 3-penten-1-ynyl, 1,3-hexadiene-5-ynyl and the like.

20 The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to a straight or branched configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy and the like.

25 The term "C₃₋₆-cycloalkoxy" as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the indicated number of carbon atoms linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of cycloalkoxy groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

30 The term "C₁₋₆-alkylthio" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₋₆-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio and the like.

 The term "C₃₋₆-cycloalkylthio" as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the indicated number of carbon atoms linked through a divalent sulfur atom having its free valence bond from the sulfur atom. Examples of

cycloalkoxy groups are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like.

The term "C₁₋₆-alkylamino" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₋₆-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino and the like.

The term "C₁₋₆-cycloalkylamino" as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the indicated number of carbon atoms linked through amino having a free valence bond from the nitrogen atom e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and the like.

The term "C₁₋₆-alkoxyC₁₋₆-alkyl" as used herein, alone or in combination, refers to C₁₋₆-alkyl as defined herein whereto is attached a C₁₋₆-alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like.

The term "aryl" as used herein refers to an aromatic monocyclic or an aromatic fused bi- or tricyclic hydrocarbon group e.g. phenyl, naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like.

The term "arylene" as used herein refers to divalent aromatic monocyclic or a divalent aromatic fused bi- or tricyclic hydrocarbon group e.g. phenylene, naphthylene and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "perhalomethoxy" means trifluoromethoxy, trichloromethoxy, tribromomethoxy or triiodomethoxy.

The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl and the like.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-7 membered monocyclic aromatic system or a 8-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl,

pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinnyl, indolyl, benzimidazolyl, benzofuranyl, pteridiny and purinyl and the like.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a
5 heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrolyloxy, imidazolyloxy, pyrazolyloxy, triazolyloxy, pyrazinyloxy, pyrimidinyloxy, pyridazinyloxy, isothiazolyloxy, isoxazolyloxy, oxazolyloxy, oxadiazolyloxy, thiadiazolyloxy, quinolinyloxy, isoquinolinyloxy, quinazolininyloxy, quinoxalinyloxy, indoltloxy, benzimidazolyloxy, benzofuranyloxy, pteridinyloxy and purinyloxy and the like.

10 The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy, 2-naphthyloxy and the like.

15 The term "aralkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphtyl)ethoxy and the like.

The term "heteroaralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-
20 1-(2-pyrimidyl)ethyl and the like.

The term "heteroaralkoxy" as used herein refers to a heteroarylalkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-
25 1-(2-pyrimidyl)ethyl linked to oxygen, and the like.

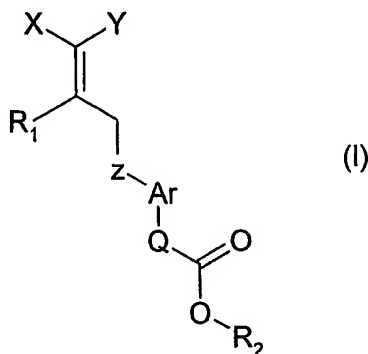
The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g. phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio and the like.

30 Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may
35 be the same or different.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula (I):



5 wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen, hydroxy, cyano, amino, C₁₋₆-alkylamino, C₁₋₆-dialkylamino, C₃₋₆-cycloalkyl-amino or carboxy; or
- C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio or C₃₋₆-cycloalkylthio each of which is optionally substituted with halo-
 10 gen; or
- aryl, aryloxy, arylthio, acyl, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl; and

15

Y is aryl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen, hydroxy, cyano, amino, C₁₋₆-alkylamino, C₁₋₆-dialkylamino, C₃₋₆-cycloalkyl amino, carboxy ; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio or C₃₋₆-cycloalkylthio each of which is optionally substituted with halo-
 20 gen; or
 - aryl, aryloxy, arylthio, acyl, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl or perhalomethoxy; or
- 25

Y is C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₄₋₆-alkenynyl; and

Ar is arylene which is optionally substituted with one or more halogen; and

Z is O or S; and

5

Q is $-(CH_2)_n-$ wherein n is 0, 1, 2 or 3; and

R₁ is hydrogen or halogen; or

10 R₁ is C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, carboxy, amino or cyano; and

R₂ is hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₄₋₆-alkenynyl or aryl;

15 provided that X and Y independently is not a pyridine ring; or

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

20 In one embodiment, the present invention is concerned with compounds of formula (I) wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen; or
 - C₁₋₆-alkyl, C₁₋₆-alkoxy, or C₁₋₆-alkylthio each of which is optionally substituted with halogen;
- 25 or

- aryl, aryloxy, arylthio, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy or heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

30 In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen; or
- aryl, aryloxy or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is aryl, which is optionally substituted with one or more substituents selected from

- halogen; or
- 5 • aryl, aryloxy or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is phenyl, which is optionally substituted with one or more substituents selected from

- 10 • bromine; or
- phenyl or phenyloxy.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is heteroaryl, which is optionally substituted with one or more substituents selected from

- 15 • halogen; or
- aryl or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is heteroaryl, which is optionally substituted with aryl.

- 20 In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is thiazolyl, which is optionally substituted with phenyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is fluorenyl.

- 25 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is aryl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen; or
- C₁₋₆-alkyl, C₁₋₆-alkoxy or C₁₋₆-alkylthio each of which is optionally substituted with halogen; or
- 30 • aryl, aryloxy, arylthio, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy or heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

- In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is aryl or heteroaryl each of which is optionally substituted with one or
- 35 more substituents selected from

- halogen; or
- C₁₋₆-alkyl, or
- aryl or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

5 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is aryl, which is optionally substituted with one or more halogens.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is phenyl, which is optionally substituted with one or more halogens.

10 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is heteroaryl, which is optionally substituted with one or more halogens.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is C₁₋₆-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is methyl.

15 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Ar is arylene, which is optionally substituted with one or more halogens.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Ar is phenylene, which is optionally substituted with one or more halogens.

20 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Z is O.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein n is 1 or 2.

25 In another embodiment, the present invention is concerned with compounds of formula (I) wherein R₁ is hydrogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein R₁ is C₁₋₃-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein R₁ is C₁₋₃-alkoxy.

30 In another embodiment, the present invention is concerned with compounds of formula (I) wherein R₂ is hydrogen or C₁₋₆-alkyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein R₂ is hydrogen, methyl or ethyl.

35 In another embodiment, the present invention is concerned with compounds of formula I wherein alkyl is methyl or ethyl.

In another embodiment, the present invention is concerned with compounds of formula I wherein alkenyl is vinyl or 1-propenyl.

In another embodiment, the present invention is concerned with compounds of formula I wherein alkynyl is 1-propynyl.

5 In another embodiment, the present invention is concerned with compounds of formula I wherein alkenynyl is 1-pentene-4-yne.

In another embodiment, the present invention is concerned with compounds of formula I wherein alkoxy is methoxy, ethoxy, isopropoxy or cyclopropoxy.

10 In another embodiment, the present invention is concerned with compounds of formula I wherein aryl is phenyl.

In another embodiment, the present invention is concerned with compounds of formula I wherein arylene is phenylene.

In another embodiment, the present invention is concerned with compounds of formula I wherein halogen is fluorine, bromine or chlorine.

15 In another embodiment, the present invention is concerned with compounds of formula I wherein perhalomethyl is trifluoromethyl.

In another embodiment, the present invention is concerned with compounds of formula I wherein heteroaryl is, thiazolyl.

20 In another embodiment, the present invention is concerned with compounds of formula I wherein aralkyl is benzyl.

In another embodiment, the present invention is concerned with compounds of formula I wherein aryloxy is phenoxy.

In another embodiment, the present invention is concerned with compounds of formula I wherein aralkoxy is benzyloxy.

25 In another embodiment, the present invention is concerned with compounds of formula I wherein the substituents R_1 and Y are arranged in a trans-configuration.

In another embodiment, the present invention is concerned with compounds of formula I wherein the substituents R_1 and Y are arranged in a cis-configuration.

30 In another embodiment, the present invention is concerned with compounds of formula I which is a PPAR δ agonist.

In another embodiment, the present invention is concerned with compounds of formula I which selective PPAR δ agonist.

Examples of specific compounds of the invention are:

35 3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid,

- 3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid ethyl ester,
3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid,
5 {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid methyl ester,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester,
10 (E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid,
(Z)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid, or
a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mix-
15 ture of optical isomers, including a racemic mixture, or any tautomeric forms.

Other examples of specific compounds of the invention are:

- (E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester,
20 (E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid, or
a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mix-
ture of optical isomers, including a racemic mixture, or any tautomeric forms.

Other examples of specific compounds of the invention are:

- (E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
25 (E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,
(E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid,
30 (E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid
ethyl ester,
(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid,
(Z)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid
ethyl ester,
35 (E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid,

- (E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,
(E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,
(Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid,
5 (E)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
(E)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid,
(Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
10 (Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid, or
a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

Other examples of compounds of the invention are:

- {4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-phenyl}-acetic acid,
15 {4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-phenyl}-acetic acid,
20 {4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
25 {4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-chloro-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-chloro-phenyl}-acetic acid,
30 {4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
35 {4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,

- {4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-bromo-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-bromo-phenyl}-acetic acid,
5 {4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
10 {4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-iodo-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-iodo-phenyl}-acetic acid,
15 {4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
3-[4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-phenyl]-propionic acid,
20 3-[4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-trifluoromethyl-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-phenyl]-propionic acid,
25 3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-chloro-phenyl]-propionic acid,
30 3-[4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-chloro-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-chloro-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-chloro-allyloxy]-phenyl]-propionic acid,
3-[4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-chloro-phenyl]-propionic acid,
3-[4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-chloro-phenyl]-propionic acid,
35 3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-chloro-phenyl]-propionic acid,

- 3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
5 3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-bromo-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-bromo-phenyl}-propionic acid,
10 3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
15 3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-iodo-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-iodo-phenyl}-propionic acid,
20 3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid, or
a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mix-
25 ture of optical isomers, including a racemic mixture, or any tautomeric forms.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids
30 as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic,
35 pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic,

palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium, zinc, calcium salts and the like. Examples of amines and organic amines include ammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N'-dibenzylethylenediamine, N-benzylphenylethylamine, N-methyl-D-glucamine, guanidine and the like. Examples of cationic amino acids include lysine, arginine, histidine and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, (R)- or (S)-phenylethylamine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acids,

aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the dia-stereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

5 Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting
10 the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active
15 pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

20 The invention also encompasses active metabolites of the present compounds.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

25 Furthermore, the invention relates to the use of compounds of the general formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such
30 as the conditions mentioned above.

In another aspect, the present invention relates to a method of treating and/or preventing Type I or Type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula I or pharmaceutically acceptable salts thereof for the

preparation of a pharmaceutical composition for the treatment and/or prevention of Type I or Type II diabetes.

In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

5 In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from IGT to Type 2 diabetes.

10 In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In another aspect, the present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

15 In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

20 In still another aspect, the present compounds are effective in decreasing apoptosis in mammalian cells such as beta cells of Islets of Langerhans.

In still another aspect, the present compounds are useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis.

25 In still another aspect, the present compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

The present compounds may also be administered in combination with one or more further pharmacologically active substances eg., selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

30 Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

15 In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

20 Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

In one embodiment of the invention the present compounds are administered in combination with insulin.

35 In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide or senaglinide.

5 In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg. miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

10 Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

15 In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicaldipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

25 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

30 The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

5 If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

10 For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

15 For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, 20 or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

25	Active compound (as free compound or salt thereof)	5 mg
	Colloidal silicon dioxide (Aerosil)	1.5 mg
	Cellulose, microcryst. (Avicel)	70 mg
	Modified cellulose gum (Ac-Di-Sol)	7.5 mg
	Magnesium stearate	Ad.

30

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

35

*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of formula (I) in combination with further pharmacologically active substances such as those described in the foregoing.

5 The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

10 The compounds of the invention are effective over a wide dosage range. A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of ad-
15 ministration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or
20 more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

Any novel feature or combination of features described herein is considered essential to this invention.

25 The present invention is further illustrated in the following representative examples which are, however, not intended to limit the scope of the invention in any way.

EXAMPLES

The compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se. The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR),
30 mass spectrometry (MS) or optical rotation. NMR shifts (δ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in $^{\circ}\text{C}$. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org.

Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). The optical rotation was measured on a Advanced Laser Polarimeter.

The abbreviations as used in the examples have the following meaning:

THF: tetrahydrofuran

5 · DMSO: dimethylsulfoxide

CDCl₃: deuterated chloroform

DMF: N,N-dimethylformamide

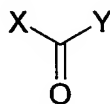
min: minutes

h: **hours**

10 General procedure (A)

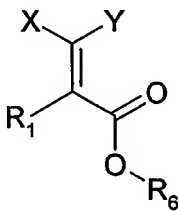
Step A:

Reacting a compound of formula II



(11)

15 wherein X and Y are defined as above, through a Wittig-like process with for example $(\text{EtO})_2\text{PO}(\text{CHR}_1)\text{COOR}_6$ (wherein R_6 is an alkyl group), in the presence of a base such as sodium hydride, EtONa and the like to give a compound of formula III



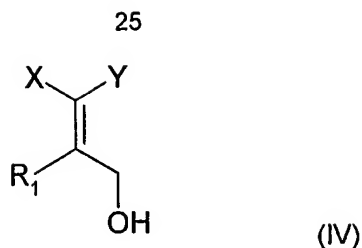
(III)

20

wherein X, Y, R₁ and R₆ are defined as above

Step B:

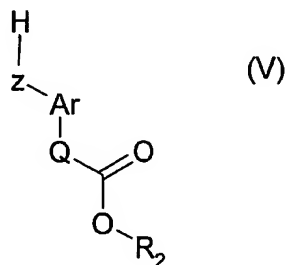
Reducing the compound of formula III, wherein X, Y, R₁ and R₆ are defined as
25 above with a suitable reagent such as diisobutylaluminium hydride, to give a compound of
formula IV



wherein X, Y and R₁ are defined as above, and

5 **Step C:**

Reacting the compound of formula IV, wherein X, Y and R₁ are defined as above, (except that when X or Y is substituted with hydroxy, amino, C₁₋₆-alkylamino or C₂₋₆-dialkylamino these functionalities have to be protected) with a compound of formula V



10

wherein Z, Ar, Q and R₂ are defined as above, except that R₂ is not hydrogen under Mitsunobu conditions, using a reagent such as triphenylphosphine/diethylazodicarboxylate and the like to obtain a compound of formula I, wherein X, Y, Z, Ar, Q, R₁ and R₂ are defined as

15 above, except that R₂ is not hydrogen.

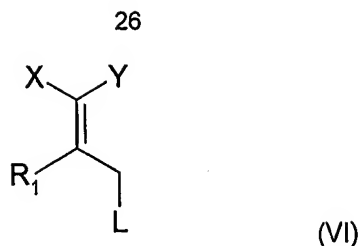
General procedure (B)

Step A:

Converting the -OH functionality in the compound of formula IV, wherein X, Y and R₁ are defined as above, to an appropriate leaving group (L) such as p-toluenesulfonate, methanesulfonate, halogen (for example by methods according to: Houben-Weyl, Methoden der organischen Chemie, Alkohole III, 6/1b, Thieme-Verlag 1984, 4th Ed., pp. 927-939; Comprehensive Organic Transformations. A guide to functional group preparations, VCH Publishers 1989, 1st Ed., pp. 353-363 and *J. Org. Chem.*, Vol. 36 (20), 3044-3045, 1971), triflate and the like, to give a compound of formula VI

20

25



wherein X, Y, R₁ and L are defined as above.

5 **Step B:**

Reacting the compound of formula VI wherein L is a leaving group such as p-toluenesulfonate, methanesulfonate, halogen, triflate and the like and wherein X, Y and R₁ are defined as above with a compound of formula V wherein Z, Ar, Q and R₂ are defined as above, except that R₂ is not hydrogen to give a compound of formula I wherein X, Y, Z, Ar, Q,

10 R₁ and R₂ are defined as above, except that R₂ is not hydrogen.

General procedure (C)

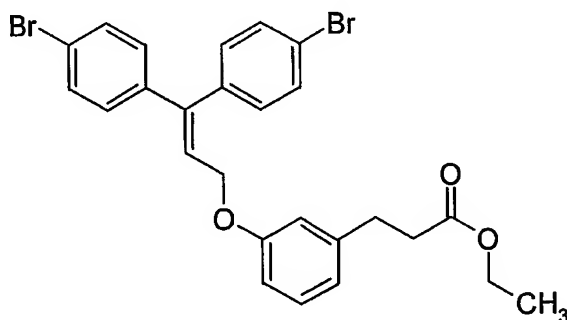
Step A:

By chemical or enzymatic saponification of a compound of formula I wherein X, Y, Z, Ar, Q, R₁ and R₂ are defined as above, except that R₂ is not hydrogen to give a compound of

15 formula I wherein X, Y, Z, Ar, Q, R₁ and R₂ are defined as above, except that R₂ is hydrogen.

Example 1 (General procedure (A))

3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester



20 **Step A:**

A solution of triethyl phosphonoacetate (26.8 g, 120.0 mmol) in dry THF (100 mL) was added at 0°C over a period of 25 min. to a stirred suspension of sodium hydride (60% in oil, 4.8 g, 120.0 mmol) in dry THF (100 ml). After stirring at 0°C for 30 min. a solution of 4,4'-

dibromobenzophenone (20.4 g, 60.0 mmol) in dry THF (200 ml) was added and the mixture slowly warmed to room temperature, and stirring continued for 48 h. The reaction mixture was diluted with 1N hydrochloric acid (400 ml) and ethyl acetate (100 ml). The organic phase was separated, and the aqueous phase further extracted with ethyl acetate (2 x 300 ml). The combined organic phases were washed with water (300 ml x 3), dried (MgSO₄), filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica gel (15% ethyl acetate in n-heptane eluent) to give 24.5 g (99%) 3,3-bis-(4-bromophenyl)-acrylic acid ethyl ester as an off-white amorphous solid.

¹H NMR (CDCl₃): δ 1.15 (3H, t), 4.05 (2H, q), 6.34 (1H, s), 7.10 (4H, dd), 7.48 (4H, dd).

10 Step B:

A 1M solution of DIBAL-H in toluene (150 ml, 150 mmol) was added dropwise, at –70°C over 30 min, to a stirred solution of 3,3-bis-(4-bromophenyl)-acrylic acid ethyl ester (24.5 g, 59.7 mmol) in dry THF (400 ml) and stirred for 30 min. The mixture was warmed to room temperature, and stirred for 1.5 h. The mixture was poured into 1N HCl (700 ml) with vigorous stirring and the product extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give the crude product as an off-white solid, which was purified by column chromatography on silica gel (15% ethyl acetate in n-heptane eluent). The purified product was diluted in boiling heptane, filtered and the filtrate cooled, giving 15.8 g (72%) 3,3-bis-(4-bromophenyl)prop-2-en-1-ol as an crystalline solid.

¹H NMR (CDCl₃): δ 1.45 (1H, t), 4.18 (2H, t), 6.23 (1H, t), 7.06 (4H, dd), 7.45 (4H, dd).

Step C:

1) To an ice-cooled solution of 3-(3-hydroxyphenyl)propionic acid (20.0 g, 120 mmol) in ethanol was dropwise added thionyl chloride (8.8 ml, 120 mmol). The mixture was stirred at room temperature over night, concentrated *in vacuo* and submitted to flash chromatography (10% ethyl acetate in toluene eluent) to give 23.3 g of 3-(3-hydroxy-phenyl)-propionic acid ethyl ester.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 2.60 (2H, t), 2.88 (2H, t), 4.13 (2H, q), 6.65-6.75 (3H, m), 7.05-7.15 (1H, m).

30

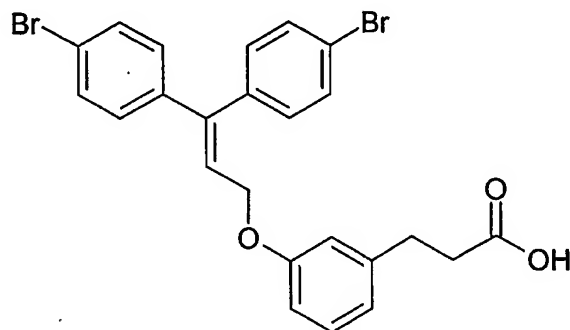
2) Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (567 mg, 2.25 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (455 mg, 2.25 mmol), 3-(3-hydroxy-phenyl)-propionic acid ethyl ester (291 mg, 1.5 mmol) and 3,3-bis-(4-bromophenyl)prop-2-en-1-ol (552 mg, 1.5 mmol) in dry THF (15 ml), the mixture warmed to

room temperature, and stirred for 48 h. The reaction mixture was concentrated in vacuo, and added water and ethyl acetate (30 ml each). The aqueous layer was collected and further extracted with ethyl acetate (2 x 30 ml). The organic layers were combined, washed with water, dried (MgSO₄) and evaporated. The crude product was then purified by column chromatography on silica (toluene eluent) to give 756 mg (93%) of the title compound.

¹H NMR (CDCl₃): δ 1.23 (3H, t), 2.57 (2H, t), 2.88 (2H, t), 4.10 (2H, q), 4.52 (2H, d), 6.30 (1H, t), 6.62-6.70 (2H, m), 6.77 (1H, d), 7.03-7.18 (5H, m), 7.48 (2H, d), 7.52 (2H, d).

Example 2 (General procedure (C))

3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid



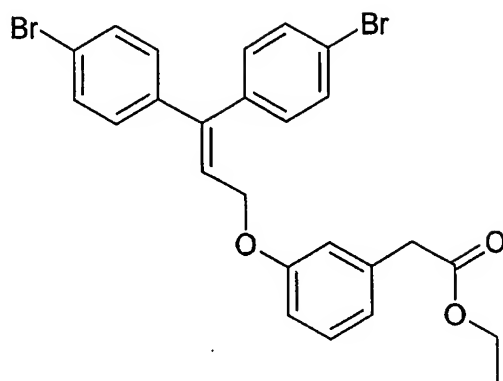
Step A:

3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 1) (755 mg, 1.4 mmol) was hydrolysed in 1N NaOH (5.6 ml) and ethanol (15 ml) for 16 h at room temperature. Water (5 ml) was added and ethanol removed by concentration *in vacuo*. The mixture was neutralised with 6N HCl. The crude product was extracted with ethyl acetate (x 3). The organic layers were combined, dried (MgSO₄) and evaporated. The residue was dissolved in toluene and the title compound precipitated with petroleum ether, to give 430 mg of the title compound.

¹H NMR (MeOD): δ 2.55 (2H, t), 2.85 (2H, t), 4.55 (2H, d), 6.35 (1H, t), 6.60-6.73 (2H, m), 6.78 (1H, d), 7.08-7.18 (5H, m), 7.45 (2H, d), 7.58 (2H, d).

Example 3 (General procedure (A))

3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid ethyl ester



Step A-B:

3,3-Bis-(4-bromophenyl)prop-2-en-1-ol was prepared as described in example 1, step A-B.

5

Step C:

1) To an ice-cooled solution of 3-(3-hydroxyphenyl)-acetic acid (21.0 g, 138 mmol) in ethanol was dropwise added thionyl chloride (10.1 ml, 138 mmol). The mixture was stirred at room temperature over night, concentrated *in vacuo* and submitted to flash chromatography (10% ethyl acetate in toluene eluent) to give 23.8 g of 3-(3-hydroxy-phenyl)-acetic acid ethyl ester.

10

^1H NMR (CDCl_3): δ 1.27 (3H, t), 3.55 (2H, s), 4.15 (2H, q), 6.11 (1H, s), 6.68-6.85 (3H, m), 7.15 (1H, t).

15

2) Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (567 mg, 2.25 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (455 mg, 2.25 mmol), 3-(3-hydroxy-phenyl)-acetic acid ethyl ester (270 mg, 1.5 mmol) and 3,3-bis-(4-bromophenyl)prop-2-en-1-ol (552 mg, 1.5 mmol) in dry THF (15 ml), the mixture warmed to room temperature, and stirred for 48 h. The reaction mixture was concentrated *in vacuo*, and added water and ethyl acetate (30 ml each). The aqueous layer was collected and further extracted with ethyl acetate (2 x 30 ml). The organic layers were combined, washed with water, dried (MgSO_4) and evaporated. The crude product was then purified by column chromatography on silica (toluene eluent) to give 701 mg (88%) of the title compound.

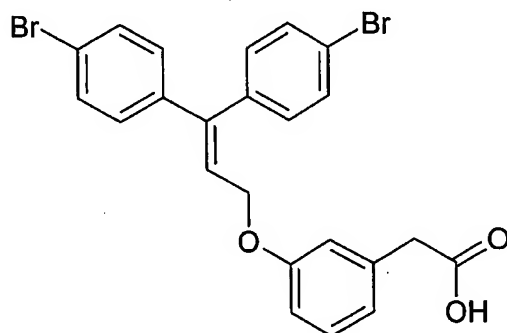
20

^1H NMR (CDCl_3): δ 1.23 (3H, t), 3.53 (2H, s), 4.13 (2H, q), 4.52 (2H, d), 6.32 (1H, t), 6.70-6.78 (2H, m), 6.87 (1H, d), 7.05-7.13 (5H, m), 7.20 (2H, t), 7.42 (2H, d), 7.52 (2H, d).

25

Example 4 (General procedure (C))

3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid



5 Step A:

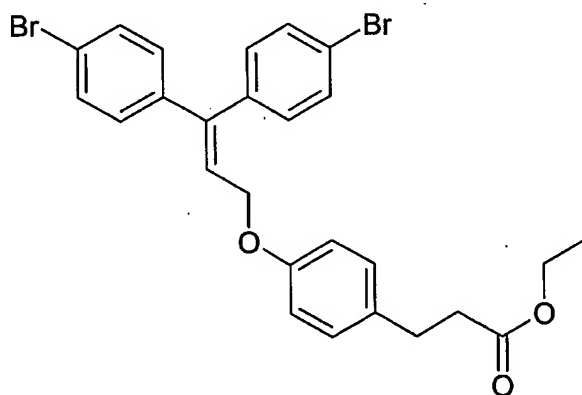
The title compound was prepared from 3-{3-[3,3-bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid ethyl ester (example 3) (701 mg, 1.3 mmol) by a procedure analogous to that described in example 2.

¹H NMR (CDCl₃): δ 3.55 (2H, s), 4.53 (2H, d), 6.30 (1H, t), 6.75 (2H, bs), 6.84 (1H, d), 7.10

10 (4H, t), 7.20 (1H, t), 7.40 (2H, d), 7.52 (2H, d).

Example 5 (General procedure (A))

3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-propionic acid ethyl ester



15 Step A-B:

3,3-Bis-(4-bromophenyl)prop-2-en-1-ol was prepared as described in example 1 step A-B.

Step C:

1) To an ice-cooled solution of 3-(p-hydroxyphenyl)-propionic acid (8.3 g, 50.0 mmol) in ethanol (100 mL) was dropwise added thionyl chloride (3.7 mL, 50.7 mmol). The mixture was stirred at room temperature over night, concentrated in vacuo and the residue purified by kugelrohr distillation, to give 9.6 g (99%) of 3-(4-hydroxy-phenyl)-propionic acid ethyl ester as a colourless oil.

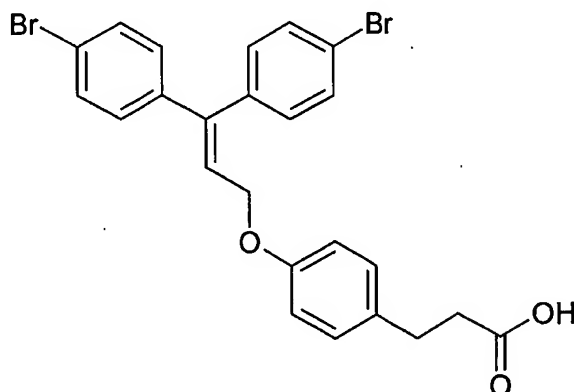
^1H NMR (CDCl_3): δ 1.21 (3H, t), 2.58 (2H, t), 2.86 (2H, t), 4.12 (2H, q), 6.75 (2H, d), 6.90 (1H, bs), 7.01 (2H, d).

2) Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (504 mg, 2.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (404 mg, 2.0 mmol), 3-(4-hydroxy-phenyl)-propionic acid ethyl ester (388 mg, 2.0 mmol) and 3,3-bis-(4-bromophenyl)prop-2-en-1-ol (736 mg, 2.0 mmol) in dry THF (50 ml), the mixture warmed to room temperature, and stirred for 4 h. The reaction mixture was concentrated in vacuo, and added water and ethyl acetate (75 ml each). The aqueous layer was collected and further extracted with ethyl acetate (2 x 75 ml). The organic layers were combined, washed with water, dried (MgSO_4) and evaporated. The crude product was then purified by column chromatography on silica (25 % ethylacetane in heptane eluent) to give 1.0 g (92%) of the title compound.

^1H NMR (CDCl_3): δ 1.23 (3H, t), 2.58 (2H, t), 2.88 (2H, t), 4.12 (2H, q), 4.52 (2H, d), 6.32 (1H, t), 6.76 (2H, d), 7.04-7.15 (6H, m), 7.42 (2H, d), 7.53 (2H, d).

Example 6 (General procedure (C))

3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-propionic acid



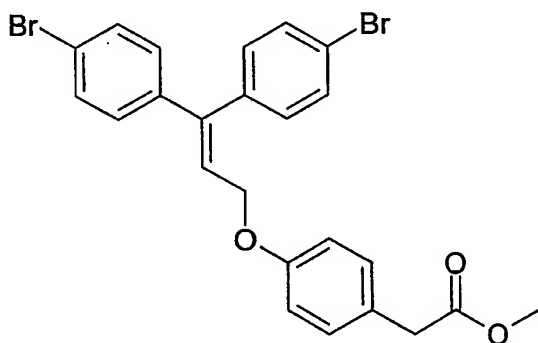
25 Step A:

To a solution of 3-{4-[3,3-bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 5) (1.0 g, 2.0 mmol) in toluene (20 mL) and ethanol (50 mL) was added 1N NaOH (10.0 mL) and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo and 1N HCl added. The product was extracted with ethyl acetate (x 3). The organic layers were combined, washed with water, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was recrystallised from warm ethanol (100 mL), which was concentrated to 60 mL, and cooled, to give 600 mg (56 %) of the title compound.

¹H NMR (CDCl₃): δ 2.65 (2H, t), 2.90 (2H, t), 4.53 (2H, d), 6.32 (1H, t), 6.76 (2H, d), 7.03-7.15 (6H, m), 7.42 (2H, d), 5.52 (2H, d).

Example 7 (General procedure (A))

{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid methyl ester



Step A-B:

3,3-Bis-(4-bromophenyl)prop-2-en-1-ol was prepared as described in example 1 step A-B.

Step C:

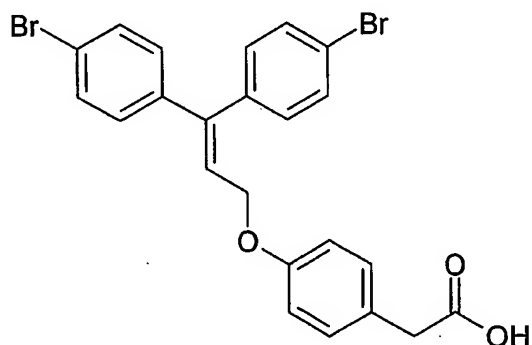
Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (504 mg, 2.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (404 mg, 2.0 mmol), methyl 4-hydroxyphenylacetate (250 mg, 1.5 mmol) and 3,3-bis-(4-bromophenyl)prop-2-en-1-ol (552 mg, 1.5 mmol) in dry THF (10 ml), the mixture stirred for 1 h, filtered and concentrated in vacuo. The crude product was then purified by column chromatography on silica (toluene eluent). The purified product was suspended in petroleum ether, filtered to give 480 mg (62%) of the title compound.

^1H NMR (CDCl_3): δ 3.55 (2H, s), 3.68 (3H, s), 4.52 (2H, d), 6.32 (1H, t), 6.78 (2H, d), 7.03-7.20 (6H, m), 7.42 (2H, d), 7.53 (2H, d).

Example 8 (General procedure (C))

{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid

5



Step A

To a solution of {4-[3,3-bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid ethyl ester (example 7) (473 mg, 0.9 mmol) in THF (5 mL) and ethanol (3 mL) was added 1N NaOH (3 mL) and the reaction mixture was stirred at 60°C for 1 h and at room temperature over night. The title compound as an sodium salt, was isolated by filtration and washed with ethanol to give 375 mg (81 %).

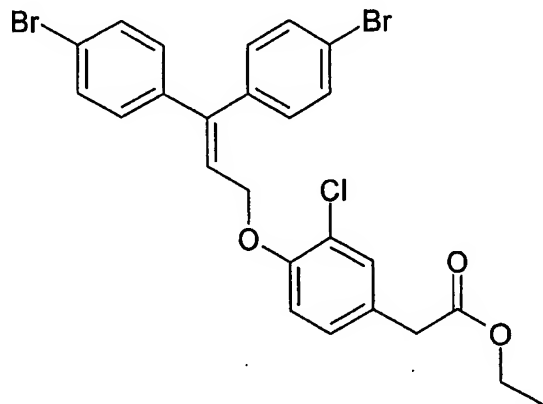
10

^1H NMR (MeOD): δ 3.40 (2H, s), 4.53 (2H, d), 6.35 (1H, t), 6.73 (2H, d), 7.08-7.25 (6H, m), 7.47 (2H, d), 5.57 (2H, d).

15

Example 9 (General procedure (A))

{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester



Step A-B:

3,3-Bis-(4-bromophenyl)prop-2-en-1-ol was prepared as described in example 1 step A-B.

5 Step C:

1) To an ice-cooled solution of 3-chloro-4-hydroxyphenylacetic acid (10.0 g, 53.0 mmol) in ethanol was dropwise added thionyl chloride (3.9 ml, 53.5 mmol). The mixture was stirred at room temperature for 48 h, concentrated in vacuo and submitted to flash chromatography (graduated from toluene to 5% ethyl acetate in toluene eluent) to give 11.0 g of 3-chloro-4-hydroxyphenylacetic acid ethyl ester.

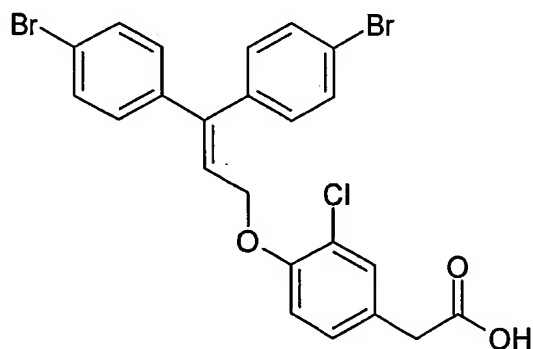
¹H NMR (CDCl₃): δ 1.27 (3H, t), 3.53 (2H, s), 4.15 (2H, q), 5.65 (1H, s), 6.95 (1H, d), 7.08 (1H, dd), 7.26 (1H, d).

2) A solution of tributylphosphine (955 µl, 3.0 mmol), 3-chloro-4-hydroxyphenylacetic acid ethyl ester (472 mg, 2.2 mmol) and 3,3-bis-(4-bromophenyl)prop-2-en-1-ol (736 mg, 2.0 mmol) in dry THF (15 ml) was stirred at 0-5°C for 30 min, under a atmosphere of nitrogen. Azodicarboxylic dipiperidide (756 mg, 3.0 mmol) was added the mixture stirred at 0-5°C for 2 h, and at room temperature over night. The reaction mixture was filtered and the filtrate concentrated in vacuo. The crude product was then purified by column chromatography on silica (eluent graduated from heptane to toluene) to give 1.0 g (89%) of the title compound.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 3.52 (2H, s), 4.14 (2H, q), 4.58 (2H, d), 6.34 (1H, t), 6.72 (1H, d), 7.03-7.14 (5H, m), 7.30 (1H, d), 7.42 (2H, d), 7.53 (2H, d).

Example 10 (General procedure (C))

25 {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid



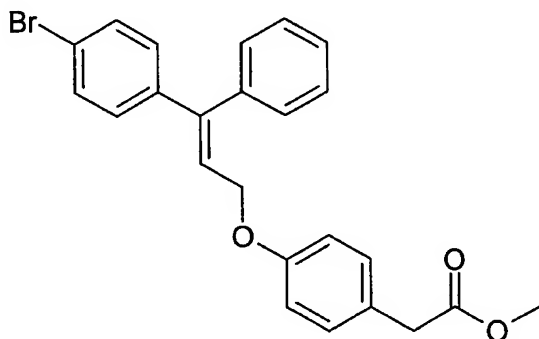
Step A:

To a solution of {4-[3,3-bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester (example 9) (1.0 g, 1.8 mmol) in THF (8 ml) and ethanol (5 ml) was added 1N NaOH (4.0 ml) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was suspended in water and 817 mg (82%) of the title compound was isolated by filtration as the sodium salt.

^1H NMR (MeOD): δ 3.37 (2H, s), 4.57 (2H, d), 6.40 (1H, t), 6.79 (1H, d), 7.07-7.20 (5H, m), 7.35 (1H, d), 7.45 (2H, d), 7.58 (2H, d).

Example 11 (General procedure (A))

(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester

**Step A:**

Sodium (5.29 g, 230 mmol) was added to ethanol (200 ml) at 20°C and the mixture stirred until the metal had fully reacted. Triethyl phosphonoacetate (30.7 ml, 153 mmol) was added, the mixture stirred for 20 min, then a solution of 4-bromobenzophenone (20.0 g, 76.6 mmol) was added and the reaction mixture heated to 70°C under reflux for 17 h. The solution was cooled, the ethanol evaporated and the residue partitioned between 4 N HCl and ethyl acetate. The aqueous layer was collected and further extracted with ethyl acetate (2 x 200 ml). The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated. This was purified by column chromatography on silica gel to give:

(Z)-3-(4-bromophenyl)-3-phenylacrylic acid ethyl ester as a white crystalline compound; 11.1 g. ^1H NMR (300 MHz, CDCl₃) δ : 1.17 (3H, t), 4.07 (2H, q), 6.37 (1H, s), 7.08 (2H, d), 7.20-7.42 (5H, m), 7.50 (2H, d); and

(E)-3-(4-bromophenyl)-3-phenylacrylic acid ethyl ester as a clear oil; 12.0 g. NMR (300 MHz, CDCl₃) δ : 1.10 (3H, t), 4.05 (2H, q), 6.34 (1H, s), 7.10-7.22 (4H, m), 7.34-7.48 (5H, m).

Step B:

A 1.2 M solution of DIBAL-H in toluene (45 ml, 42 mmol) was added dropwise, at –15°C over 20 min, to a stirred solution of (E)-3-(4-bromophenyl)-3-phenylacrylic acid ethyl ester (6.0 g, 18.1 mmol) in dry THF (80 ml), and the mixture stirred for 30 min. Rochelles salt and water was carefully added, and the resulting mixture extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give 5.2 g of (E)-3-(4-bromo-phenyl)-3-phenyl-prop-2-en-1-ol.

¹H NMR (300 MHz, CDCl₃) δ: 1.40 (1H, br s), 4.22 (2H, d), 6.23 (1H, t), 7.06-7.18 (4H, m), 7.32-7.45 (5H, m).

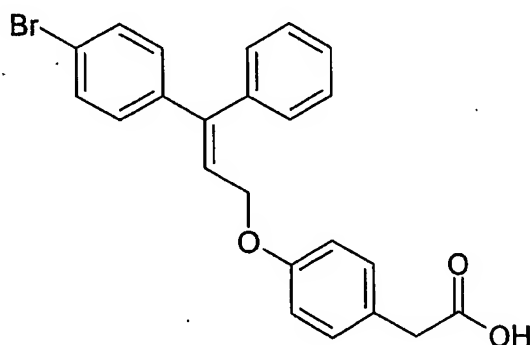
Step C:

Azodicarboxylic dipiperidine (0.756 g, 3.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (0.94 ml, 786 mg, 3.0 mmol), methyl 4-hydroxyphenylacetate (332 mg, 2.0 mmol) and (E)-3-(4-bromo-phenyl)-3-phenyl-prop-2-en-1-ol (578 mg, 2.0 mmol) in dry THF (25 ml), the mixture was stirred for 1h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (toluene as eluent) to give 710 mg (81%) of the title compound.

¹H NMR (300 MHz, CDCl₃) δ: 3.54 (2H, s), 3.67 (3H, s), 4.55 (2H, d), 6.30 (1H, t), 6.78 (2H, d), 7.10-7.22 (6H, m), 7.35-7.43 (5H, m).

Example 12 (General procedure (C))

(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid

**Step A:**

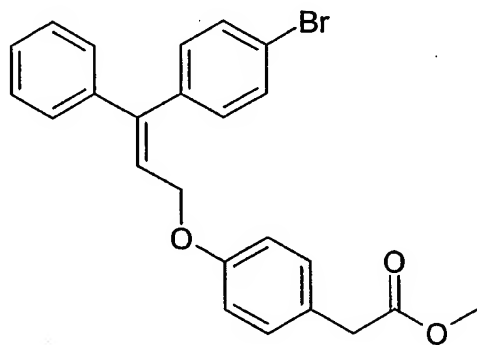
To a solution of (E)-{4-[3-(4-bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid ethyl ester (example 11) (700 mg, 1.6 mmol) in THF (5 ml) and ethanol (5 ml) was added 1N NaOH (5.0 ml) and the reaction mixture was stirred for 1 h at 60°C for 1h and at room tem-

perature over night. The reaction mixture was added water and the organic solvent evaporated. 1 N HCl was added to pH ~1-2 and the product extracted with dichloromethane/isopropanol (19:1). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The residue was suspended in toluene/petroleum ether (1:1) and 490 mg (70%) of the title compound was isolated by filtration.

¹H NMR (CDCl₃): δ 3.57 (2H, s), 4.5 (2H, d), 6.30 (1H, t), 6.79 (2H, d), 7.08-7.22 (6H, m), 7.35-7.45 (5H, m).

Example 13 (General procedure (A))

(Z)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester



Step A:

(Z)-3-(4-bromophenyl)-3-phenylacrylic acid ethyl ester was prepared as described in example 11 step A.

Step B:

A 1.2 M solution of DIBAL-H in toluene (84 ml, 100 mmol) was added dropwise, at -15°C over 20 min, to a stirred solution of (Z)-3-(4-bromophenyl)-3-phenylacrylic acid ethyl ester (11.1 g, 33.5 mmol) in dry THF (150 ml), and the mixture stirred for 30 min. Rochelles salt and water was carefully added, and the resulting mixture extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give 9.3 g of (Z)-3-(4-bromo-phenyl)-3-phenyl-prop-2-en-1-ol.

¹H NMR (300 MHz, CDCl₃) δ: 1.40 (1H, br s), 4.22 (2H, d), 6.23 (1H, t), 7.06-7.18 (4H, m), 7.32-7.45 (5H, m).

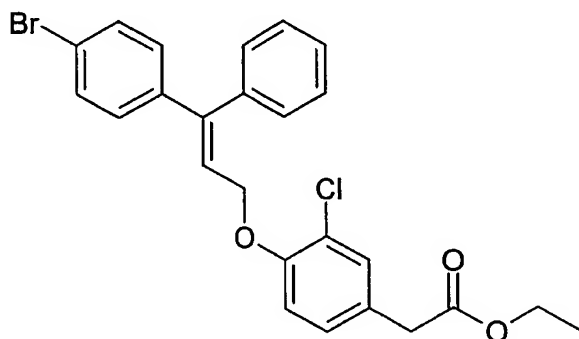
Step C:

Azodicarboxylic dipiperidide (0.756 g, 3.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (0.94 ml, 786 mg, 3.0 mmol), methyl 4-hydroxyphenylacetate (332 mg, 2.0 mmol) and (Z)-3-(4-bromo-phenyl)-3-phenyl-prop-2-en-1-ol (578 mg, 2.0 mmol) in dry THF (25 ml), the mixture was stirred for 1h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (toluene as eluent) to give 650 mg (74%) of the title compound.

¹H NMR (300 MHz, CDCl₃) δ : 3.55 (2H, s), 3.68 (3H, s), 4.54 (2H, d), 6.33 (1H, t), 6.80 (2H, d), 7.10 (2H, d), 7.16 (2H, d), 7.20-7.32 (5H, m), 7.53 (2H, d).

Example 14 (General procedure (A))

(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester



Step A-B:

(E)-3-(4-Bromo-phenyl)-3-phenyl-prop-2-en-1-ol was prepared as described in example 11 step a-b.

Step C:

1) To an ice-cooled solution of 3-chloro-4-hydroxyphenyl-acetic acid (10.0 g, 53 mmol) in ethanol was dropwise added thionyl chloride (3.9 mL, 53.5 mmol). The mixture was stirred at room temperature over night, concentrated *in vacuo* and submitted to flash chromatography (eluent: graduated from 10 % ethyl acetate in toluene to toluene) to give 11 g of 3-chloro-4-hydroxyphenyl-acetic acid ethyl ester.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 3.52 (2H, s), 4.15 (2H, q), 5.75 (1H, s), 6.93 (1H, d), 7.05 (1H, d), 7.25 (1H, s).

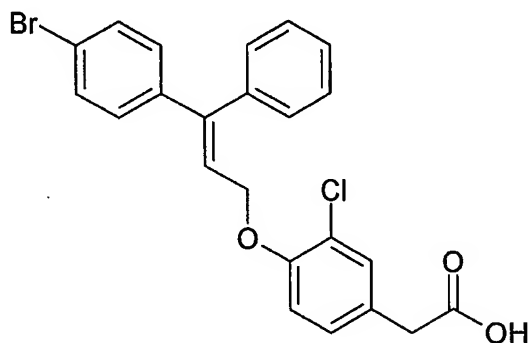
2) Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (756 mg, 3.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (786 mg, 3.0 mmol), 3-chloro-4-

hydroxyphenyl-acetic acid ethyl ester (537 mg, 2.5 mmol) and (E)-3-(4-bromo-phenyl)-3-phenyl-prop-2-en-1-ol (578 mg, 2.0 mmol) in dry THF (15 ml), the mixture was stirred for 2 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica (eluent: toluen) to give 640 mg (66%) of the title compound.

- 5 ^1H NMR (CDCl_3): δ 1.25 (3H, t), 3.50 (2H, s), 4.14 (2H, q), 4.53 (2H, d), 6.33 (1H, t), 6.70 (1H, d), 7.03 (1H, dd), 7.13 (2H, d), 7.15-7.22 (2H, m), 7.30 (1H, d), 7.35-7.45 (5H, m).

Example 15 (General procedure (C))

(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid



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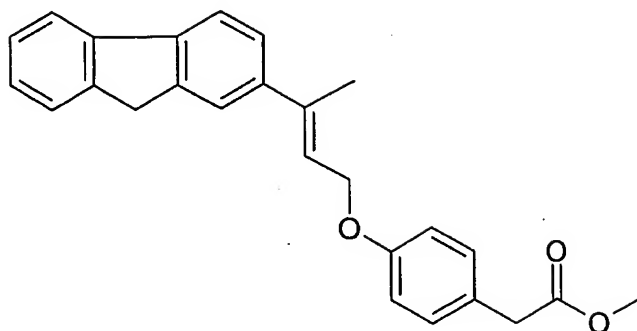
Step A

The title compound was prepared from (E)-{4-[3-(4-bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester (example 14) (640 mg, 1.3 mmol) by a procedure analogous to that described in example 12.

- 15 ^1H NMR (CDCl_3): δ 3.53 (2H, s), 4.63 (2H, d), 6.33 (1H, t), 6.68 (1H, d), 7.03 (1H, dd), 7.08-7.22 (4H, m), 7.30 (1H, d), 7.35-7.45 (5H, m).

Example 16 (General procedure (A))

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester

**Step A:**

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester was prepared from 2-acetylfluorene and triethylphosphonoacetate by a procedure analogous to that described in example 11-A.

¹H NMR (CDCl₃): δ 1.32 (3H, t), 2.63 (3H, s), 3.90 (2H, s), 4.23 (2H, q), 6.22 (2H, d), 7.28-7.42 (4H, m), 7.54 (4H, dt), 7.68 (2H, d), 7.78 (4H, t).

Step B:

A 1M solution of DIBAL-H in toluene (15 ml, 15 mmol) was added dropwise, at -70°C over 30 min, to a stirred solution of (E)-{4-[3-(9H-fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester (2.0 g, 7.2 mmol) in dry THF (100 ml) and stirred for 30 min. The mixture was warmed to room temperature, and stirred for 1.5 h. The mixture quenched with methanol (2 mL), added 1N HCl (30 ml) and the product extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give the crude (E)-3-(9H-fluoren-2-yl)-but-2-en-1-ol.

¹H NMR (CDCl₃): δ 2.13 (3H, s), 3.90 (2H, s), 4.40 (2H, s), 6.05 (1H, t), 7.22-7.42 (2H, m), 7.45 (1H, d), 7.54 (1H, d), 7.60 (1H, s), 7.75 (2H, dd)

Step C:

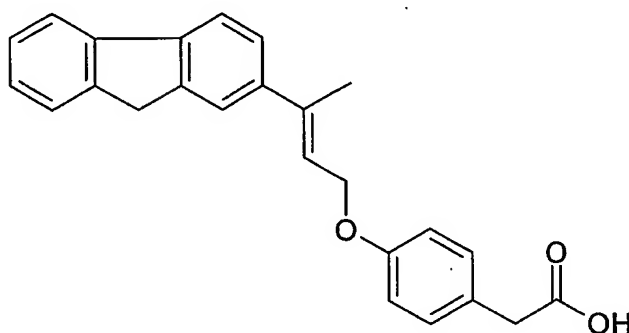
Under a atmosphere of nitrogen, methyl 4-hydroxyphenylacetate (183 mg, 1.1 mmol) was added to a stirred cooled solution of azodicarboxylic dipiperidide (378 mg, 1.5 mmol), tributylphosphine (304 mg, 1.5 mmol) and (E)-3-(9H-fluoren-2-yl)-but-2-en-1-ol (236 mg, 1.0 mmol) in dry benzene (30 ml), the mixture warmed to room temperature, and stirred for 17 h. The reaction mixture was diluted with water (100 ml) and ethyl acetate (100 ml each). The aqueous layer was collected and further extracted with ethyl acetate (2 x 50 ml). The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated. The

crude product was then purified by column chromatography on silica (eluent: 15 % ethyl acetate in toluene) to give 240 mg (62%) of the title compound.

¹H NMR (CDCl₃): δ 2.19 (3H, s), 3.58 (2H, s), 3.69 (3H, s), 3.90 (2H, s), 4.76 (2H, d), 6.11 (1H, t), 6.92 (2H, d), 7.21 (2H, d), 7.30 (1H, d), 7.37 (1H, t), 7.45 (1H, d), 7.54 (1H, d), 7.62 (1H, s), 7.73 (2H, dd).

Example 17 (General procedure (C))

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid



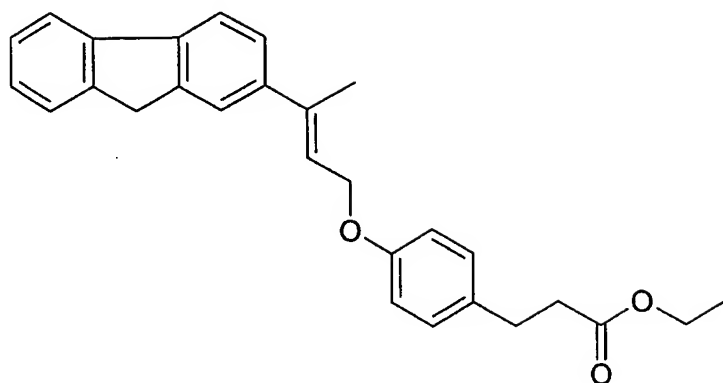
10 Step A:

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester (example 16) (193 mg, 0.5 mmol) was suspended in 1N NaOH (5.0 mL) and methanol (5 mL) and stirred for 16 h at room temperature. A 2nd portion and 1N NaOH was added and stirring continued for 24 h. The mixture was concentrated to 10 mL volume then diluted with 1N HCl (50 mL) and ethyl acetate (150 mL). The aqueous layer was separated and extracted with ethyl acetate (50 mL). The organic layers were combined, dried (NaSO₄) and evaporated. The residue was recrystallised from ethyl acetate (50 ml) to give 140 mg (75 %) of the title compound as a pale yellow powder.

¹H NMR (DMSO): δ 2.17 (3H, s), 3.49 (2H, s), 3.93 (2H, s), 4.78 (2H, d), 6.11 (1H, s), 6.94 (2H, d), 7.18 (2H, d), 7.31 (1H, dt), 7.38 (1H, t), 7.50 (1H, d), 7.58 (1H, d), 7.70 (1H, s), 7.87 (2H, t).

Example 18 (General procedure (A))

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester

**Step A-B:**

(E)-3-(9H-Fluoren-2-yl)-but-2-en-1-ol was prepared as described in example 16 step

A-B.

5

Step C:

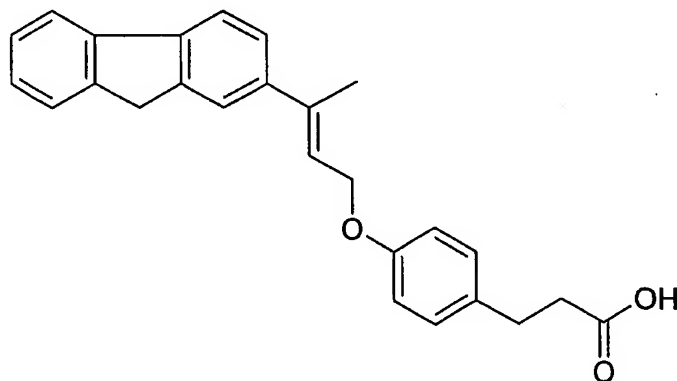
The title compound was prepared from 3-(4-hydroxy-phenyl)-propionic acid ethyl ester (example 5, step C-1) (213 mg, 1.1 mmol) and (E)-3-(9H-fluoren-2-yl)-but-2-en-1-ol (235 mg, 1.0 mmol) by a procedure analogous to that described in example 16-step C.

10 ¹H NMR (CDCl₃): δ 1.25 (3H, t), 2.18 (3H, s), 2.60 (2H, t), 2.90 (2H, t), 3.90 (2H, s), 4.12 (2H, q), 4.75 (2H, d), 6.10 (1H, t), 6.89 (2H, d), 7.13 (2H, d), 7.30 (1H, d), 7.38 (1H, t), 7.45 (1H, d), 7.53 (1H, d), 7.63 (1H, s), 7.75 (2H, dd).

Example 19 (General procedure (C))

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid

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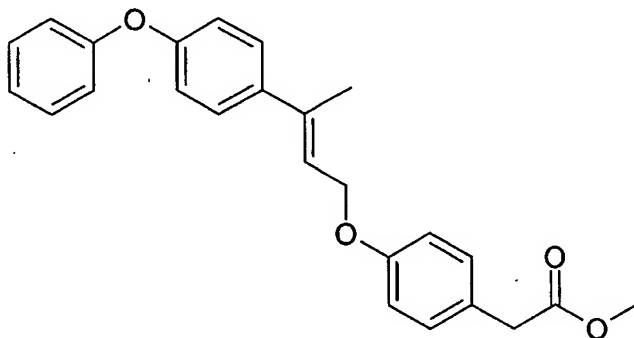
Step A:

(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester (example 18) (220 mg, 0.53 mmol) was suspended in 1N NaOH (5.5 ml) and methanol (20 ml) and stirred for 24 h at room temperature. The mixture was diluted with 1N HCl (50 ml) and ethyl acetate (50 mL). The aqueous layer was separated and extracted with ethyl acetate (50 ml) 5 The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated. The residue was recrystallised from boiling ethanol (20 ml) to give 150 mg (73 %) of the title compound.

¹H NMR (DMSO): δ 2.16 (3H, s), 2.76 (2H, t), 3.93 (2H, s), 4.76 (2H, d), 6.10 (1H, t), 6.91 10 (2H, d), 7.14 (2H, d), 7.28-7.40 (2H, m), 7.50 (1H, d), 7.58 (2H, d), 7.69 (1H, s), 7.87 (2H, t).

Example 20 (General procedure (A))

(E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester

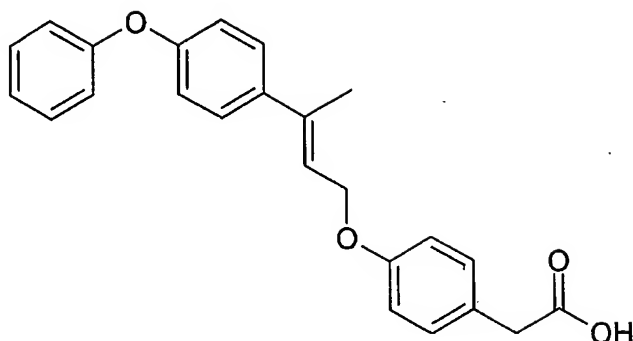
**Step A-C:**

The title compound was prepared from 4-phenoxyacetophenone (12.0 g, 0.056 mol) by a sequence analogous to that described in example 22 step A-C, to give 168 mg (44%) of the title compound

¹H NMR (CDCl₃): δ 2.12 (3H, s), 3.57 (2H, s), 3.68 (3H, s), 4.72 (2H, d), 6.02 (1H, t), 6.9-7.5 20 (13H, m).

Example 21 (General procedure (C))

(E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid

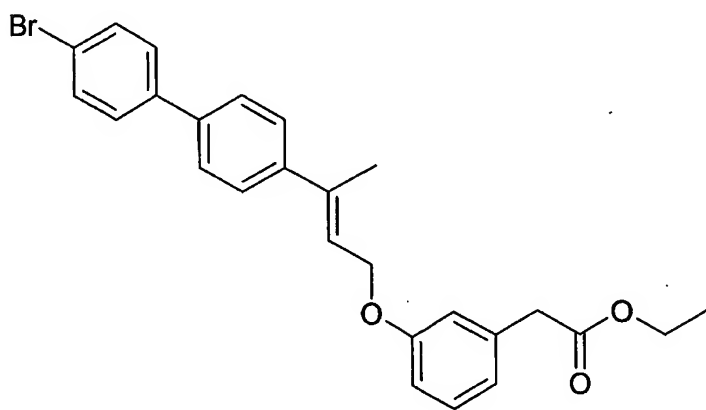
**Step A:**

(E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester (example 20 (150 mg, 0.4 mmol) was suspended in 1N NaOH (1 mL) and ethanol (5 mL) and stirred for 24 h at room temperature. The mixture was diluted with 1N HCl (1 mL) and ethyl acetate (10 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated to give 116 mg (80 %) of the title compound.

¹H NMR (DMSO): δ 2.10 (3H, s), 3.57 (2H, s), 4.74 (2H, d), 6.01 (1H, t), 6.9-7.2 (9H, m), 7.35-7.5 (4H, m).

Example 22 (General procedure (A))

(E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester

**Step A:**

(E)-3-(4'-Bromo-biphenyl-4-yl)-but-2-enoic acid ethyl ester was prepared from 4-(4-bromophenyl)acetophenone (12.0 g, 0.044 mol), sodium (1.25 g, 0.052 mol) and triethyl phosphonoacetate (11.73 g, 0.052 mol) by a procedure analogous to that described in example 11 step A, yielding 11.97 g (80%).

¹H NMR (300 MHz, CDCl₃) δ: 1.32 (3H, t), 2.61 (3H, d), 4.23 (2H, q), 6.19 (1H, d), 7.40-7.58 (8H, m).

Step B:

5 (E)-3-(4'-bromo-biphenyl-4-yl)-but-2-en-1-ol was prepared from (E)-3-(4'-bromo-biphenyl-4-yl)-but-2-enoic acid ethyl ester (3.45 g, 10.0 mmol) and DIBAL-H (1M in toluene, 40 mL, 40 mmol) by a procedure analogous to that described in example 11 step B, yielding 1.68 g (55%).

¹H NMR (300MHz, CDCl₃) δ: 2.14 (3H, d), 4.4 (2H, t), 6.05 (1H, dt), 7.45-7.55 (8H, m).

10

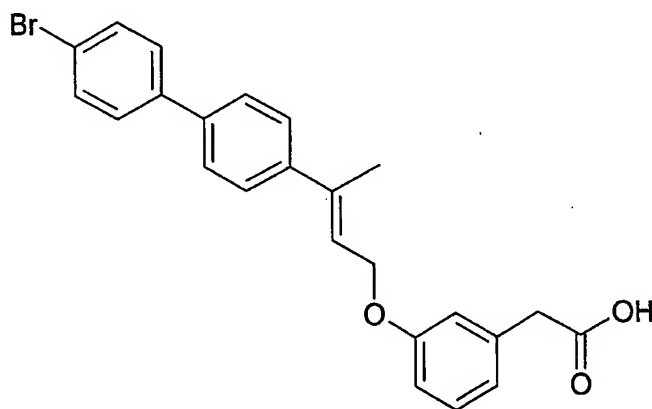
Step C:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidine (353 mg, 1.4 mmol) was added at 0-5 °C to a stirred solution of tributylphosphine (0.4 mL, 1.4 mmol), ethyl 3-hydroxyphenylacetate (120 mg, 0.7 mmol) and (E)- 3-(4'-bromo-biphenyl-4-yl)-but-2-en-1-ol
15 (200 mg, 0.7 mmol) in dry THF (10 ml), the mixture stirred for 16 h, filtered and concentrated in vacuo. The crude product was then purified by column chromatography on silica (eluent: 20 % ethyl acetate in heptane) to give 168 mg (44%) of the title compound.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 2.17 (3H, s), 3.59 (2H, s), 4.14 (2H, q) 4.77 (2H, d), 6.11 (1H, t), 6.85-8.90 (3H, m), 7.23 (1H, m), 7.45-7.57 (8H, m).

20 **Example 23** (General procedure (C))

(E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid



Step A:

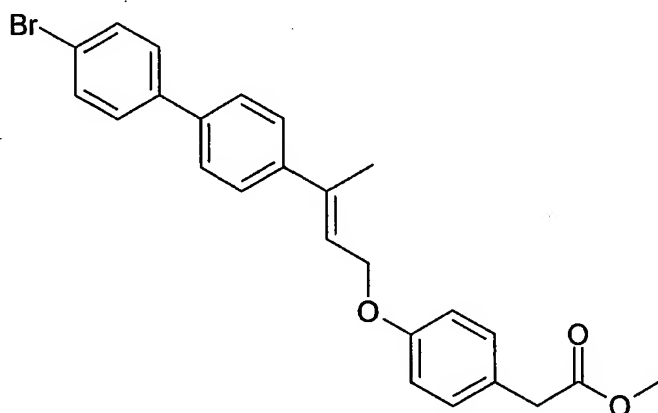
25 (E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester (example 22) (150 mg, 0.32 mmol) was suspended in 1N NaOH (0.82 mL) and ethanol (5

mL) and stirred for 24 h at room temperature. The mixture was diluted with 1N HCl (0.82 mL) and ethyl acetate (10 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL). The organic layers were combined, washed with brine, dried (MgSO_4) and evaporated to give 138 mg (98 %) of the title compound.

5 ^1H NMR (DMSO): δ 2.13 (3H, s), 3.54 (2H, s), 4.78 (2H, d), 6.12 (1H, t), 6.83-6.9 (3H, m), 7.23 (1H, m), 7.56-7.68 (8H, m).

Example 24 (General procedure (A))

(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester



10

Step C:

Under an atmosphere of nitrogen, azodicarboxylic dipiperidide (353 mg, 1.4 mmol) was added at 0-5 °C to a stirred solution of tributylphosphine (0.4 mL, 1.4 mmol), methyl 4-hydroxyphenylacetate (110 mg, 0.7 mmol) and (E)- 4-(4'-Bromo-biphenyl-4-yl)-but-2-en-1-ol (example 22 step A-B)(200 mg, 0.7 mmol) in dry THF (10 mL), the mixture stirred for 16 h, filtered and concentrated in vacuo. The crude product was then purified by column chromatography on silica (eluent: 20 % ethyl acetate in heptane) to give 264 mg (84%) of the title compound.

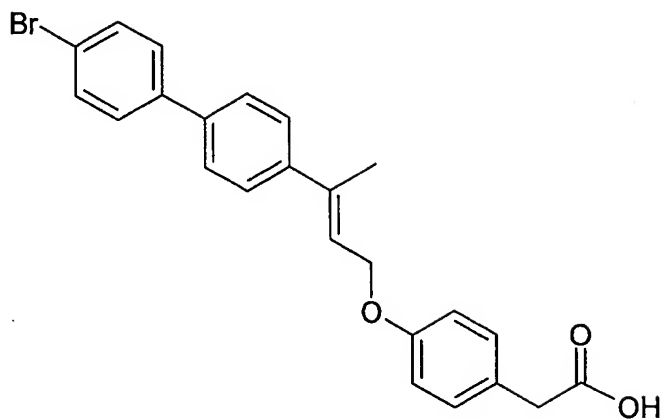
15

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^1H NMR (CDCl_3): δ 2.12 (3H, s), 3.58 (2H, s), 3.68 (3H, s), 4.76 (2H, d), 6.12 (1H, t), 6.8-6.9 (3H, m), 7.23 (1H, m), 7.56-7.68 (8H, m).

Example 25 (General procedure (C))

(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid

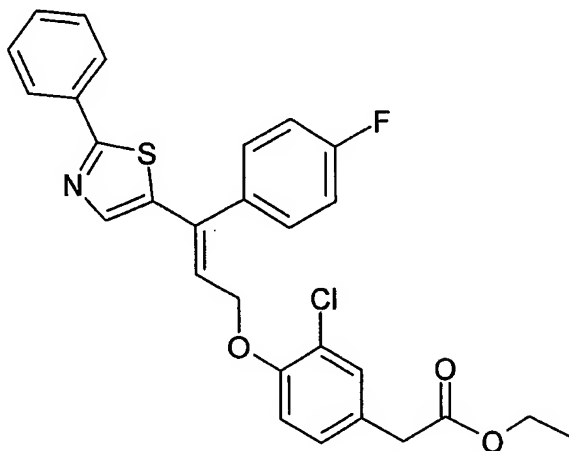
**Step A:**

(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester (example 24) (210 mg, 0.58 mmol) was suspended in 1N NaOH (1.16 mL) and ethanol (5 mL) and stirred for 24 h at room temperature. The mixture was diluted with 1N HCl (1.16 mL) and ethyl acetate (10 mL). The aqueous layer was separated and extracted with ethyl acetate (30 L) The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated to give 141 mg (55 %) of the title compound.

¹H NMR (DMSO): δ 2.14 (3H, s), 3.53 (2H, s), 4.78 (2H, d), 6.10 (1H, t), 6.8-6.9 (3H, m), 7.23 (1H, m), 7.53-7.72 (8H, m).

Example 26 (General procedure (A))

(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid ethyl ester

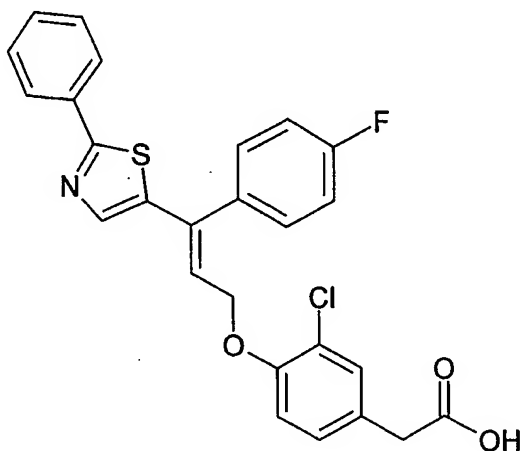
**Step A-C:**

The title compound was prepared by a method analogous to that described in example 14, using (4-fluorophenyl)-(2-phenyl-1,3-thiazol-5-yl)-methanone as starting material.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 3.52 (2H, s), 4.15 (2H, q), 4.53 (2H, d), 6.40 (1H, t), 6.70 (1H, d), 7.03-7.20 (3H, m), 7.24-7.38 (4H, m), 7.40-7.48 (3H, m), 7.93 (2H, dd).

5 **Example 27** (General procedure (C))

(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid



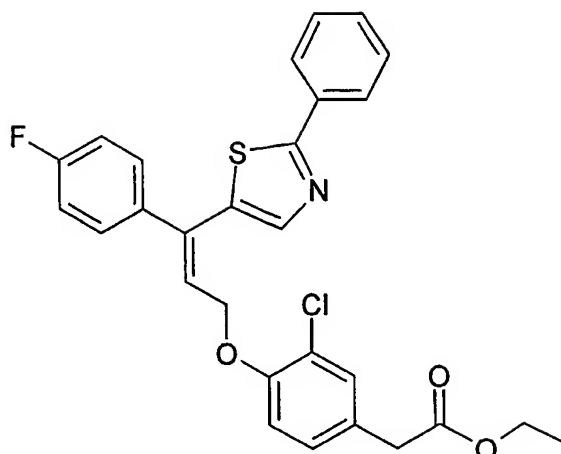
Step A:

- 10 The title compound was prepared by a method analogous to that described in example 2, using (E)-{3-chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid ethyl ester (example 26) as starting material.

¹H NMR (MeOD): δ 3.50 (2H, s), 5.53 (2H, d), 6.43 (1H, t), 6.78 (1H, d), 7.08 (1H, dd), 7.13-7.23 (2H, m), 7.25-7.38 (4H, m), 7.40-7.50 (3H, m), 7.85-7.95 (2H, m).

15 **Example 28** (General procedure (A))

(Z)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid ethyl ester

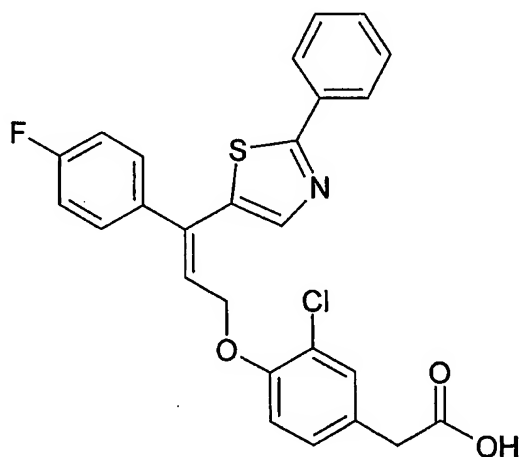
**Step A-C:**

The title compound was prepared by a method analogous to that described in example 14, using (4-fluorophenyl)-(2-phenyl-1,3-thiazol-5-yl)-methanone as starting material.

- 5 ^1H NMR (CDCl_3): δ 1.25 (3H, t), 3.52 (2H, s), 4.15 (2H, q), 4.85 (2H, d), 6.35 (1H, t), 6.84 (1H, d), 7.0-7.18 (3H, m), 7.28-7.40 (4H, m), 7.40-7.48 (3H, m), 7.90-7.98 (2H, m).

Example 29 (General procedure (C))

(E)-{3-Chloro-4-[3-(4-fluorophenyl)-3-(2-phenylthiazol-5-yl)-allyloxy]-phenyl}-acetic acid



10

Step A:

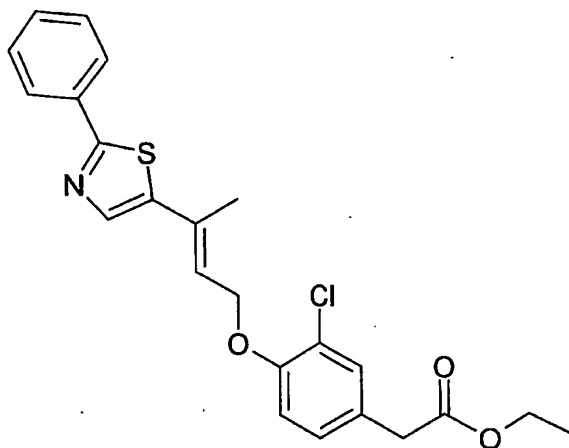
The title compound was prepared by a method analogous to that described in example 2, using (Z)-{3-chloro-4-[3-(4-fluorophenyl)-3-(2-phenylthiazol-5-yl)-allyloxy]-phenyl}-acetic acid ethyl ester (example 28) as starting material.

^1H NMR (MeOD): δ 3.53 (2H, s), 6.40 (1H, t), 6.98 (1H, d), 7.03-7.25 (3H, m), 7.28-7.50 (7H, m), 7.88-7.95 (2H, m).

Example 30 (General procedure (A))

(E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester

5



Step A-C:

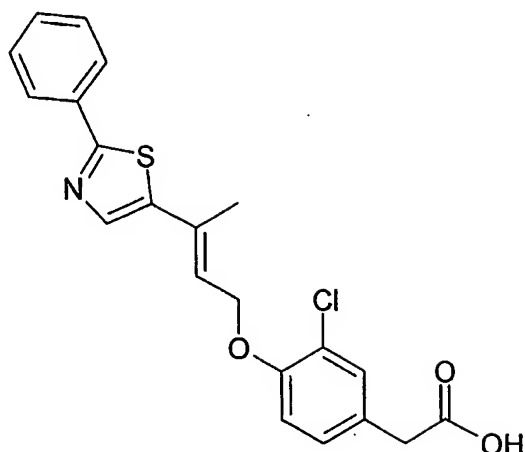
The title compound was prepared by a method analogous to that described in example 14, using 1-(2-phenyl-thiazol-5-yl)-ethanone as starting material.

10 ^1H NMR (CDCl_3): δ 1.25 (3H, t), 2.19 (3H, s), 3.52 (2H, s), 4.15 (2H, q), 4.78 (2H, d), 6.17 (1H, t), 6.90 (1H, d), 7.15 (1H, d), 7.34 (1H, s), 7.38-7.48 (3H, m), 7.75 (1H, s), 7.88-7.80 (2H, m).

Example 31 (General procedure (C))

(E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid

15

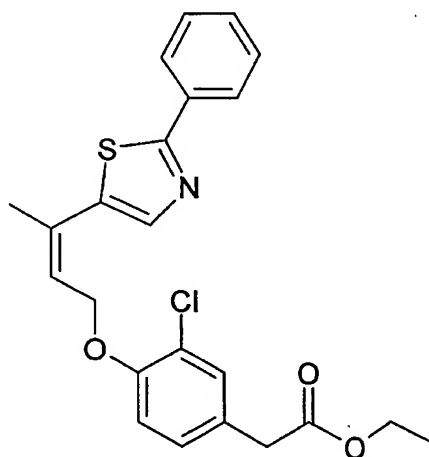
**Step A:**

The title compound was prepared by a method analogous to that described in example 2, using (E)-{3-chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester (example 30) as starting material.

¹H NMR (CDCl₃): δ 2.18 (3H, s), 3.55 (2H, s), 4.78 (2H, d), 6.15 (1H, t), 6.90 (1H, d), 7.13 (1H, dd), 7.33 (1H, d), 7.38-7.47 (3H, m), 7.79 (1H, s), 7.85-7.93 (2H, m).

Example 32 (General procedure (A))

(Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester

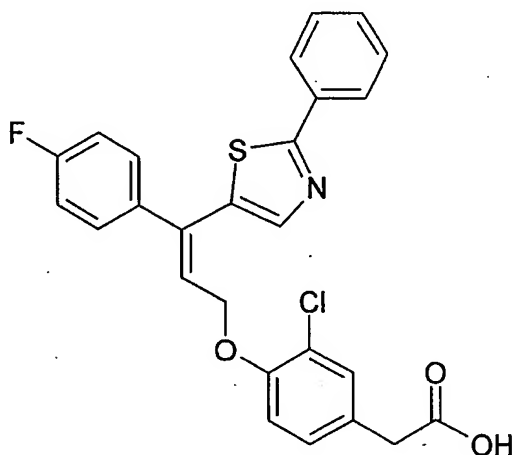
**Step A-C:**

The title compound was prepared by a method analogous to that described in example 14, using 1-(2-phenyl-thiazol-5-yl)-ethanone as starting material.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 2.25 (3H, s), 3.52 (2H, s), 4.15 (2H, q), 4.80 (2H, d), 5.95 (1H, t), 6.82 (1H, d), 7.10 (1H, dd), 7.32 (1H, d), 7.40-7.50 (3H, m), 7.75 (1H, s), 7.90-7.98 (2H, m).

Example 33 (General procedure (C))

5 (Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid



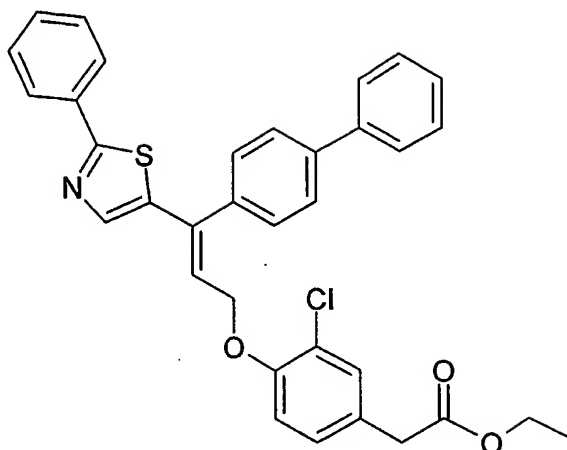
Step A:

The title compound was prepared by a method analogous to that described in ex-
10 ample 2, using (Z)-{3-chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid
ethyl ester (example 32) as starting material.

¹H NMR (CDCl₃): δ 2.25 (3H, s), 3.55 (2H, s), 4.79 (2H, d), 5.96 (1H, t), 6.83 (1H, d), 7.12 (1H, dd), 7.32 (1H, d), 7.40-7.50 (3H, m), 7.79 (1H, s), 7.88-7.97 (2H, m).

Example 34 (General procedure (A))

15 (E)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester

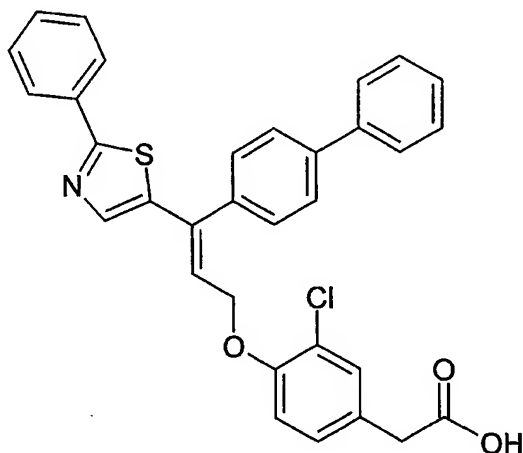
**Step A-C:**

The title compound was prepared by a method analogous to that described in example 14, using (1,1'-biphenyl)-4-yl-(2-phenyl-1,3-thiazol-5-yl)-methanone as starting material.

¹H NMR (CDCl₃): δ 1.25 (3H, t), 3.52 (2H, s), 4.15 (2H, q), 4.63 (2H, d), 6.43 (1H, t), 6.75 (1H, d), 7.15 (1H, dd), 7.30 (1H, d), 7.35-7.54 (9H, m), 7.64-7.70 (4H, m), 7.88-7.98 (2H, m).

Example 35 (General procedure (C))

(E)-4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl]-acetic acid

**Step A:**

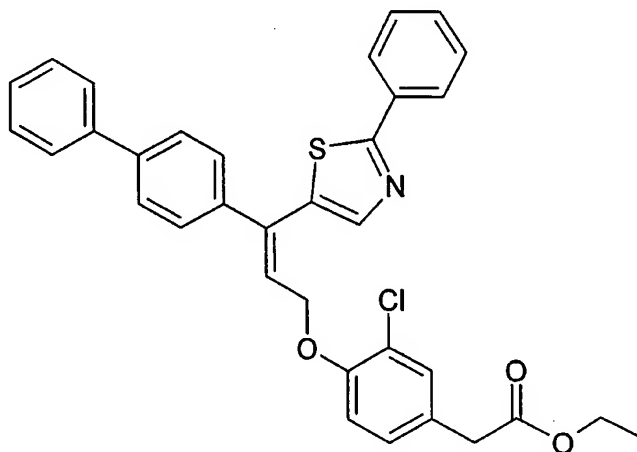
The title compound was prepared by a method analogous to that described in example 2, using (E)-4-[3-biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl]-acetic acid ethyl ester (example 34) as starting material.

^1H NMR (CDCl_3): δ 3.54 (2H, s), 4.63 (2H, d), 6.42 (1H, t), 6.73 (1H, d), 7.15 (1H, dd), 7.32 (1H, dd), 7.35-7.53 (9H, m), 7.62-7.79 (4H, m), 7.87-7.93 (2H, m).

Example 36 (General procedure (A))

(Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl

5 ester



Step A-C:

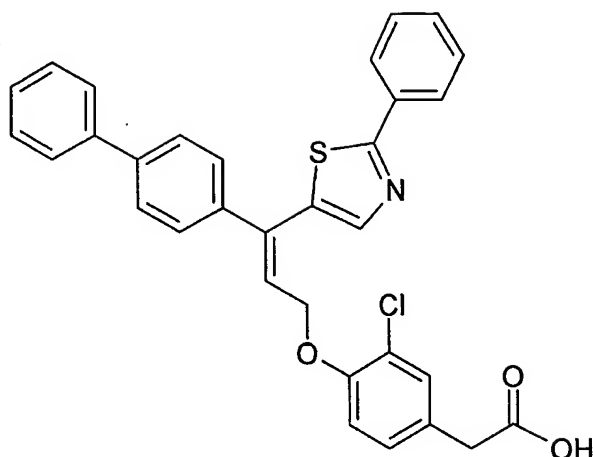
10 The title compound was prepared by a method analogous to that described in example 14, using (1,1'-biphenyl)-4-yl-(2-phenyl-1,3-thiazol-5-yl)-methanone as starting material.

^1H NMR (CDCl_3): δ 1.25 (3H, t), 3.52 (2H, s), 4.15 (2H, q), 4.87 (2H, d), 6.44 (1H, t), 6.85 (1H, d), 7.09 (1H, dd), 7.32 (1H, d), 7.37 (1H, d), 7.40-7.52 (8H, m), 7.53-7.65 (4H, m), 7.90-7.98 (2H, m).

15 **Example 37** (General procedure (C))

(Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid

55

**Step A:**

The title compound was prepared by a method analogous to that described in example 2, using (Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester (example 36) as starting material.

¹H NMR (CDCl₃): δ 3.55 (2H, s), 4.88 (2H, d), 6.44 (1H, t), 6.87 (1H, d), 7.12 (1H, dd), 7.32 (1H, d), 7.35 (1H, d), 7.40-7.50 (7H, m), 7.55-7.65 (4H, m), 7.82 (1H, s), 7.90-7.97 (2H, m).

PHARMACOLOGICAL METHODS**In vitro PPARalpha, PPARgamma and PPARdelta activation activity**

The PPAR transient transactivation assays are based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein is a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR-LBD moiety harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will direct the chimeric protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The

amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

CELL CULTURE AND TRANSFECTION

- HEK293 cells were grown in DMEM + 10% FCS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 50-80 % at transfection. A total of 0,8 µg DNA containing 0,64 µg pM1α/γLBD, 0,1 µg pCMVβGal, 0,08 µg pGL2(Gal4)₆ and 0,02 µg pADVANTAGE was transfected per well using FuGene transfection reagent according to the manufacturers instructions (Roche). Cells were allowed to express protein for 48 h followed by addition of compound.
- 10 Plasmids: Human PPAR α, γ and δ was obtained by PCR amplification using cDNA synthesized by reverse transcription of mRNA from human liver, adipose tissue and placenta respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The ligand binding domain (LBD) of each PPAR isoform was generated by PCR (PPARα: aa 167 - C-terminus; PPARγ: aa 165 - C-terminus; PPARδ: aa 128 - C-terminus) and fused to the DNA binding domain (DBD) of the yeast transcription factor GAL4 by subcloning fragments in frame into the vector pM1 (Sadowski et al. (1992), Gene 118, 137) generating the plasmids pM1αLBD, pM1γLBD and pM1δ. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the GAL4 recognition sequence (5 x CGGAGTACTGTCCTCCG(AG)) (Webster et al. (1988), Nucleic Acids Res. 16, 8192) into the vector pGL2 promotor (Promega) generating the plasmid pGL2(GAL4)₅.
- 20 pCMVβGal was purchased from Clontech and pADVANTAGE was purchased from Promega.

IN VITRO TRANSACTIVATION ASSAY

- Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Compounds were tested in quadruple in concentrations ranging from 0.001 to 300 µM. Cells were treated with compound for 24 h followed by luciferase assay. Each compound was tested in at least two separate experiments.
- 25

- Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg⁺⁺ and Ca⁺⁺ was added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting on a Packard LumiCounter. To measure β-galactosidase activity 25 µl supernatant from each transfection lysate was transferred to a
- 30

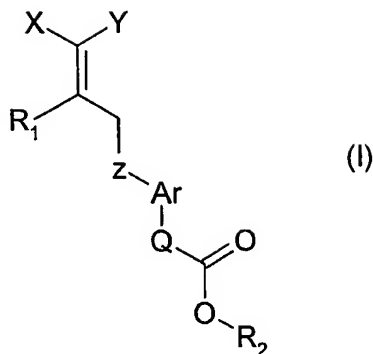
new microplate. β -galactosidase assays were performed in the microwell plates using a kit from Promega and read in a Labsystems Ascent Multiscan reader. The β -galactosidase data were used to normalize (transfection efficiency, cell growth etc.) the luciferase data.

STATISTICAL METHODS

- 5 The activity of a compound is calculated as fold induction compared to an untreated sample. For each compound the efficacy (maximal activity) is given as a relative activity compared to Wy14,643 for PPAR α , Rosiglitazone for PPAR γ and Carbacyclin for PPAR δ . The EC50 is the concentration giving 50% of maximal observed activity. EC50 values were calculated via non-linear regression using GraphPad PRISM 3.02 (GraphPad Software, San
- 10 Diego, Ca). The results were expressed as means \pm SD.

CLAIMS

1. A compound of formula (I)



- 5 wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from
- halogen, hydroxy, cyano, amino, C₁₋₆-alkylamino, C₁₋₆-dialkylamino, C₃₋₆-cycloalkyl-amino or carboxy; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio or C₃₋₆-cycloalkylthio each of which is optionally substituted with halo-
 10 gen; or
 - aryl, aryloxy, arylthio, acyl, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl; and

15

Y is aryl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen, hydroxy, cyano, amino, C₁₋₆-alkylamino, C₁₋₆-dialkylamino, C₃₋₆-cycloalkyl amino, carboxy ; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio or C₃₋₆-cycloalkylthio each of which is optionally substituted with halo-
 20 gen; or
 - aryl, aryloxy, arylthio, acyl, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl or perhalomethoxy; or
- 25

Y is C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₄₋₆-alkenynyl; and

Ar is arylene which is optionally substituted with one or more halogen; and

Z is O or S; and

5

Q is $-(CH_2)_n-$ wherein n is 0, 1, 2 or 3; and

R₁ is hydrogen or halogen; or

10 R₁ is C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, carboxy, amino or cyano; and

R₂ is hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₄₋₆-alkenynyl or aryl;

15 provided that X and Y independently is not a pyridine ring; or

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

20

2. A compound according to claim 1 wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen; or
- C₁₋₆-alkyl, C₁₋₆-alkoxy, or C₁₋₆-alkylthio each of which is optionally substituted with
- 25 halogen; or
- aryl, aryloxy, arylthio, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy or heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

30 3. A compound according to claim 1 or 2 wherein X is aryl, fluorenyl or heteroaryl each of which is optionally substituted with one or more substituents selected from

- halogen; or
- aryl, aryloxy or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.

35

4. A compound according to any one of the claims 1-3 wherein X is aryl, which is optionally substituted with one or more substituents selected from
- halogen; or
 - aryl, aryloxy or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.
- 5
5. A compound according to claim 4 wherein X is phenyl, which is optionally substituted with one or more substituents selected from
- bromine; or
 - phenyl or phenyloxy.
- 10
6. A compound according to any one of the claims 1-3 wherein X is heteroaryl, which is optionally substituted with one or more substituents selected from
- halogen; or
 - aryl or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.
- 15
7. A compound according to claim 6 wherein X is heteroaryl, which is optionally substituted with aryl.
- 20
8. A compound according to claim 7 wherein X is thiazolyl, which is optionally substituted with phenyl.
9. A compound according to any one of the claims 1-3 wherein X is fluorenyl.
- 25
- 10: A compound according to any one of the preceding claims wherein Y is aryl or heteroaryl each of which is optionally substituted with one or more substituents selected from
- halogen; or
 - C₁₋₆-alkyl, C₁₋₆-alkoxy or C₁₋₆-alkylthio each of which is optionally substituted with halogen; or
 - aryl, aryloxy, arylthio, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy or heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.
- 30

11. A compound according to claim 10 wherein Y is aryl or heteroaryl each of which is optionally substituted with one or more substituents selected from
- halogen; or
 - C₁₋₆-alkyl, or
 - 5 • aryl or heteroaryl each of which is optionally substituted with halogen, perhalomethyl, perhalomethoxy or C₁₋₆-alkyl.
12. A compound according to any one of the claims 10-11 wherein Y is aryl, which is optionally substituted with one or more halogens.
- 10 13. A compound according to claim 12 wherein Y is phenyl, which is optionally substituted with one or more halogens.
14. A compound according to any one of the claims 10-11 wherein Y is heteroaryl, which is
- 15 optionally substituted with one or more halogens.
15. A compound according to any one of the preceding claims wherein Y is C₁₋₆-alkyl.
16. A compound according to claim 15 wherein Y is methyl.
- 20 17. A compound according to any one of the preceding claims wherein Ar is arylene, which is optionally substituted with one or more halogens.
18. A compound according to claim 17 wherein Ar is phenylene, which is optionally
- 25 substituted with one or more halogens.
19. A compound according to any one of the preceding claims wherein Z is O.
20. A compound according to any one of the preceding claims wherein n is 1 or 2.
- 30 21. A compound according to any one of the preceding claims wherein R₁ is hydrogen.
22. A compound according to any one of the preceding claims wherein R₁ is C₁₋₃-alkyl.
- 35 23. A compound according to any one of the preceding claims wherein R₁ is C₁₋₃-alkoxy.

24. A compound according to any one of the preceding claims wherein R_2 is hydrogen or C_{1-8} -alkyl.
- 5 25. A compound according to claim 24 wherein R_2 is hydrogen, methyl or ethyl.
26. The compound according to any one of the preceding claims which is:
- 3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid,
10 3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid ethyl ester,
3-{3-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-propionic acid,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid methyl ester,
15 {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid,
20 (Z)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid ethyl ester,
(E)-{4-[3-(4-Bromo-phenyl)-3-phenyl-allyloxy]-3-chloro-phenyl}-acetic acid, or
a pharmaceutically acceptable salt thereof.
- 25 27. The compound according to any one of the preceding claims 1-25, which is:
- (E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester,
(E)-{4-[3-(9H-Fluoren-2-yl)-but-2-enyloxy]-phenyl}-propionic acid, or
30 a pharmaceutically acceptable salt thereof.
28. The compound according to any one of the preceding claims 1-25, which is:
- (E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4-Phenoxy-phenyl)-but-2-enyloxy]-phenyl}-acetic acid,
35 (E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,

- (E)-{3-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid methyl ester,
(E)-{4-[3-(4'-Bromo-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid
5 ethyl ester,
(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid,
(Z)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid
ethyl ester,
(E)-{3-Chloro-4-[3-(4-fluoro-phenyl)-3-(2-phenyl-thiazol-5-yl)-allyloxy]-phenyl}-acetic acid,
10 (E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,
(E)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid ethyl ester,
(Z)-{3-Chloro-4-[3-(2-phenyl-thiazol-5-yl)-but-2-enyloxy]-phenyl}-acetic acid,
(E)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl
15 ester,
(E)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid,
(Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid ethyl
ester,
(Z)-{4-[3-Biphenyl-4-yl-3-(2-phenyl-thiazol-5-yl)-allyloxy]-3-chloro-phenyl}-acetic acid, or
20 a pharmaceutically acceptable salt thereof.

29. The compound according to any one of the preceding claims 1-25, which is:
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl}-acetic acid,
25 {4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
30 {4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
35 {4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,

- {4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-chloro-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
5 {4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
10 {4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-bromo-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
15 {4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
20 {4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-iodo-allyloxy]-phenyl}-acetic acid,
{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
25 {4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-acetic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl}-propionic acid,
30 3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl)-4-yl-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-propionic acid,
35 3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-phenyl}-propionic acid,

- 3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
5 3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-chloro-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
10 3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-chloro-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
15 3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-bromo-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
20 3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-bromo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-fluoro-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
25 3-{4-[3,3-Bis-(4-iodo-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-trifluoromethyl-phenyl)-3-iodo-allyloxy]-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-cyano-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-biphenyl]-4-yl-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
30 3-{4-[3,3-Bis-(4-furan-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-2-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid,
3-{4-[3,3-Bis-(4-thiophen-3-yl-phenyl)-allyloxy]-3-iodo-phenyl}-propionic acid, or
a pharmaceutically acceptable salt thereof.

30. A compound according to any one of the preceding claims 1-29, which is a PPAR δ agonist.

31. A compound according to claim 30, which is a selective PPAR δ agonist.

5

32. The use of a compound according to any one of the preceding claims 1-31 as a pharmaceutical composition.

33. A pharmaceutical composition comprising, as an active ingredient, at least one
10 compound according to any one of the preceding claims 1-31 together with one or more pharmaceutically acceptable carriers or excipients.

34. A pharmaceutical composition according to claim 33 in unit dosage form, comprising
15 from about 0.05 mg to about 1000 mg, preferably from about 0.1 to about 500 mg of and especially preferred from about 0.5 mg to about 200 mg per day of compound according to any one of the preceding claims 1-31.

35. A pharmaceutical composition for the treatment and/or prevention of conditions
20 mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising a compound according to any one of the preceding claims 1-31 together with one or more pharmaceutically acceptable carriers or excipients.

36. A pharmaceutical composition for the treatment and/or prevention of type I diabetes,
25 type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the preceding claims 1-31 together with one or more pharmaceutically acceptable carriers or excipients.

37. A pharmaceutical composition according to any one of the claims 33-36 for oral, nasal,
30 transdermal, pulmonal, or parenteral administration.

30

38. Use of a compound according to any one of the preceding claims 1-31 for the
preparation of a pharmaceutical composition for the treatment and/or prevention of
conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated
35 Receptors (PPAR).

35

39. Use of a compound according to any one of the preceding claims 1-31 for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes, Type 2 diabetes, dyslipidemia, syndrome X (including the metabolic syndrome, i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity),
5 cardiovascular diseases (including atherosclerosis) and hypercholesteremia.
40. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound
10 according to any one of the preceding claims 1-31 or a pharmaceutical composition comprising the same.
41. A method for the treatment and/or prevention of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity, the method comprising
15 administering to a subject in need thereof an effective amount of a compound according to any one of the preceding claims 1-31 or of a pharmaceutical composition comprising the same.
42. The method according to claims 40 or 41 wherein the effective amount of the compound
20 according to any one of the preceding compound claims 1-31 is in the range of from about 0.05 mg to about 1000 mg, preferably from about 0.1 to about 500 mg of and especially preferred from about 0.5 mg to about 200 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/DK 02/00471

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C59/58 C07C69/734 A61K31/192 A61K31/216 A61P1/18
A61P3/06 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL [Online] FILE HCAPLUS; NAKAMURA ET AL : "Preparation and formulation of substituted ethylene compounds as inflammation inhibitors." retrieved from STN, accession no. 128:3548 Database accession no. 1997:752915 XP002902761 abstract & WO 97 43241 A (NIPPON SHINYAKU CO LTD) 20 November 1997 (1997-11-20) ---	1-4, 10-13, 17-19, 21,24, 25,30-37
X	WO 00 63153 A (NOVO NORDISK AS) 26 October 2000 (2000-10-26) the whole document --- -/--	1-42

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"8" document member of the same patent family

Date of the actual completion of the international search

27 September 2002

Date of mailing of the international search report

13. 11. 2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00471

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 55085 A (NOVO NORDISK AS) 2 August 2001 (2001-08-02) the whole document	1-42
A	EP 0 098 690 A (TAKEDA CHEMICAL INDUSTRIES LTD) 18 January 1984 (1984-01-18) the whole document	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00471

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 40-42
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: 38, 40
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 02/00471

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